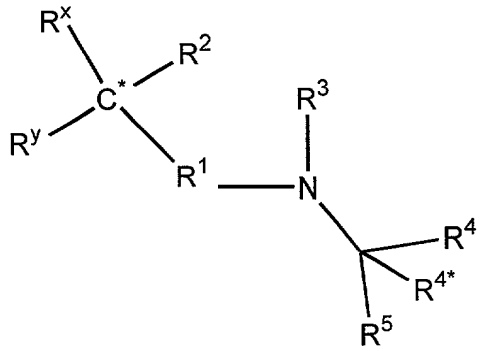
APPENDIX A: HIGHLIGHTED LEAD CLAIM 43

43. A compound of the following formula:



or a pharmaceutically acceptable salt thereof,

wherein:

(1) C^* is a substituted carbon;

(2) R^2 (a) is hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy, cyano, (C2-C7) alkanoyl, aminocarbonyl, (C1-C6) alkylaminocarbonyl, or dialkylaminocarbonyl wherein each alkyl is independently C1 to C6, (b) comprises (where R^1 is not aminoethylene, -O-R^8 or -S-R^{8*}) hydroxy, fluoro, chloro, bromo or (C2-C7) alkanoyloxy, (c) forms a double bond with an adjacent carbon or nitrogen from one of either R^1, R^{xb} or R^{yb}, (d) is R^{2a} linked by R^{2b} to C*, or (e) is ethylene forming a third bridging structure as set forth in (2^{iii})(b)(i);

(2^{i}) R^x is R^{xa} linked by R^{xb} to C^*;

(2^{ii}) R^y is R^{ya} linked by R^{yb} to C^*;

(2^{iii}) **R^{xa} and R^{ya}, are independently Ar, which is phenyl or naphthyl, heteroaryl, or or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and R^{2a}, when present, is Ar, and wherein**:

(a) **heteroaryl comprises thienyl, furanyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or one of the foregoing fused to phenyl, or methylenedioxyphenyl,**

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(b) each of R^{xa} and R^{ya} can be independently substituted with one of R^q, R^rO- or R^sS-, **wherein each of R^q, R^r and R^s are independently Ar, heteroaryl, adamantyl, or a 5 to 7-membered non-aromatic ring having from 0 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen**, and

(c) R^{xa}, R^{ya}, R^{2a}, R^q, R^r and R^s can be substituted or additionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, nitro, hydroxy, cyano, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C12) alkyl, (C2-C12) alkenyl, amino, (C1-C6) alkylamino, dialkylamino wherein each alkyl of dialkylamino is independently C1 to C6, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be substituted for hydrogen with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino wherein the amidino can be independently substituted with up to three (C1-C6) alkyl groups, wherein:

(i.) the substitutions of $R^{xa}$and R^{ya} can be combined to form a second bridge between R^{xa} and R^{ya} comprising (1) methylene or ethylene, which methylene or ethylene can be substituted by an R^2 when R^2 is ethylene to form the third bridging structure, or (2) -CH=CH-, **or (3) sulfur, or (4) oxygen**, or wherein R^{xa} and R^{ya} can be directly linked by a single bond,

(d) wherein at least one of R^{xa}, R^{ya}, R^q, R^r or R^s is heteroaryl, or a second bridge between R^{xa} and R^{ya} comprises sulfur or oxygen as set forth below, or Ar substituted with a methylenedioxy;

(2^{iv}) R^{xb} and R^{2b} are independently a single bond or (C1-C2) alkylene;

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(2^{v}) R^{yb} is a single bond, oxy, (C1-C2) alkylene, ethenylene or -CH= (where the double bond is with C*), thio, methyleneoxy or methylenethio, or either -N(R^{6}) or -CH_2-N(R^{6*})-, wherein R^{6} and R^{6*} are hydrogen or (C1-C6) alkyl;

(3) R^{1} comprises: a straight-chained (C2-C3) aliphatic group; =N-O-(ethylene), wherein the unmatched double bond is linked to C*; -O-R^{8} or -S-R^{8*} wherein R^{8} or R^{8*} is a ethylene or ethenylene and O or S is bonded to C*; aminoethylene where the amino is bonded to C*:

wherein R^{1} can be substituted with up to one hydroxy, up to one (C1-C6) alkoxy or up to one (C2-C7) alkanoyloxy, with up to two independent (C1-C6) alkyl, with up to one oxo, up to one (C1-C6) alkylidene, with the proviso that the hydroxy, alkoxy, alkanoyloxy or oxo substituents are not bonded to a carbon that is bonded to a nitrogen or oxygen;

wherein if R^{1} contributes a heteroatom linked to C*, then R^{yb} does not contribute a heteroatom linked to C*; and

wherein the alkyl or alkylidene substituents of R^{1} can be linked to form a 3 to 7-membered non-aromatic ring;

(4) R^{3} **(a)** is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{xa}, **(b)** is -R^{12}C(R^{xx})(R^{yy})(R^{11}), wherein R^{12} is bonded to N , R^{xx} is independently the same as R^{x}, R^{yy} is independently the same as R^{y}, R^{11} is independently the same as R^{2} and R^{12} is independently the same as R^{1};

(5) R^{4} and R^{4*} are independently hydrogen or (C1-C6) alkyl, or one of R^{4} and R^{4*} can be (C1-C6) hydroxyalkyl; and

(6) R^{5} is (CO)N$R^{13}R^{14}$, (CO)OR^{15}, (CO)SR^{16}, (SO_2)N$R^{17}R^{18}$, (PO)(OR^{19})(OR^{20}), (CR^{22})(OR^{23})(OR^{24}), CN or tetrazol-5-yl, wherein (a) R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} R^{19}

and R^{20} are independently hydrogen, (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of R^{15} or the sulfur of R^{16} has no more than secondary branching, (C2-C6) hydroxyalkyl, aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyls, Ar-alkyl wherein the alkyl is C1-C6, or Ar, and (b) R^{22} is hydrogen or OR^{25} and R^{23} , R^{24} and R^{25} are independently (C1-C6) alkyl, phenyl, benzyl or acetyl or, the alkyls of R^{23} and R^{24} can be combined to include 1,3-dioxolane or 1,3-dioxane:

wherein the phenyl or naphthyl groups of R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{22}, R^{23} or R^{24} can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7) alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, or amidino that can substituted with up to three (C1-C6) alkyl;

wherein R^{13} and R^{14} together with the attached nitrogen can form a 5 to 7-membered ring.

44. **The compound of claim 43, wherein at least one of R^{xa}, R^{ya}, R^{q}, R^{r} and R^{s} is thienyl or furanyl.**

45. The compound of claim 43, wherein **at least one of R^{xa} and R^{ya} is thienyl or furanyl.**

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47. The compound of claim 46, wherein at least one of **R^{xa}, R^{ya}, R^{q}, R^{r} and R^{s}** is substituted with fluoro, trifluoromethyl, trifluoromethoxy, nitro, cyano, or (C3-C8) alkyl.

53. The compound of claim 51, wherein **R^5 is (CO)OR^{15}** and R^{15} is (C2-C6) alkyl, (C2-C4) hydroxyalkyl, phenyl, phenylalkyl wherein the alkyl is C1-C3, or aminoalkyl where the alkyl is C2-C6 and the amino can be substituted with up to two independent (C1-C3) alkyls, wherein the phenyl or the phenyl of phenylalkyl can be substituted.

54. The compound of claim 51, wherein **R^5 is (CO)OR^{15}** and R^{15} is hydrogen.

62. **The compound of claim 43, wherein R3 is hydrogen, (C1-C6) alkyl, or phenyl or phenylalkyl wherein the alkyl is C1 to C6 and the phenyl or phenyl of phenylalkyl can be substituted with the same substituents defined above for the phenyl of R^{xa}.**

66. The compound of claim 43 wherein:

(1) R^2 is hydrogen,

(2) R^{xa} and R^{ya} are phenyl, **thienyl or furanyl, and can be substituted,**

(3) R^{xb} is a single bond and R^{yb} is a single bond or oxy, and

(4) R^5 is (CO)N$R^{13}R^{14}$ or (CO)OR^{15}, wherein R^{13}, R^{14}, and R^{15} are independently hydrogen; (C1-C8) alkyl which can include a (C3-C8) cycloalkyl, wherein the carbon linked to the oxygen of OR^{15} has no more than secondary branching; (C2-C6) hydroxyalkyl or aminoalkyl where the alkyl is C2 to C6 and the amino can be substituted with up to two independent (C1-C6) alkyl or phenylalkyl, wherein the alkyl is C1-C6 and the phenyl can be substituted with substituents selected from the group consisting of fluoro, chloro, bromo, nitro, cyano, hydroxy, trifluoromethyl, amidosulfonyl which can have up to two independent (C1-C6) N-alkyl substitutions, (C1-C6) alkyl, (C2-C6) alkenyl, (C1-C6) alkylamine, dialkylamine wherein each alkyl is independently C1 to C6, amino, (C1-C6) alkoxy, (C2-C7)

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alkanoyl, (C2-C7) alkanoyloxy, trifluoromethoxy, hydroxycarbonyl, (C2-C7) alkyloxycarbonyl, aminocarbonyl that can be N-substituted with up to two independent (C1-C6) alkyl, (C1-C6) alkylsulfonyl, amidino that can substituted with up to three (C1-C6) alkyl.

67. **The compound of claim 66, wherein R^2 forms a double bond with an adjacent carbon from R^1.**

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Application papers not suitable for publication

SN 09-757-011 Mail Date 01-09-01

- ☐ Non-English Specification
- ☒ Specification contains drawing(s) on page(s)_____ or table(s) 62-63
- ☐ Landscape orientation of text ☐ Specification ☐ Claims ☐ Abstract
- ☐ Handwritten ☐ Specification ☐ Claims ☐ Abstract
- ☐ More than one column ☐ Specification ☐ Claims ☐ Abstract
- ☐ Improper line spacing ☐ Specification ☐ Claims ☐ Abstract
- ☐ Claims not on separate page(s)
- ☐ Abstract not on separate page(s)
- ☐ Improper paper size -- Must be either A4 (21 cm x 29.7 cm) or 8-1/2"x 11"
  - ☐ Specification page(s)_____ ☐ Abstract
  - ☐ Drawing page(s)_____ ☐ Claim(s)
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  - ☐ Drawing page(s)_____ ☐ Claim(s)
- ☐ Not reproducible

  Reason
  - ☐ Paper too thin
  - ☐ Glossy pages
  - ☐ Non-white background

  Section
  - ☐ Specification page(s)_____
  - ☐ Drawing page(s)_____
  - ☐ Abstract
  - ☐ Claim(s)
- ☐ Drawing objection(s)
  - ☐ Missing lead lines, drawing(s)_____
  - ☐ Line quality is too light, drawing(s)_____
  - ☐ More than 1 drawing and not numbered correctly
  - ☐ Non-English text, drawing(s)_____
  - ☐ Excessive text, drawing(s)_____
  - ☐ Photographs capable of illustration, drawing(s)_____

3,3,3-tris(4-chlorophenyl)propanol *p*-toluenesulfonate [prepared by $LiAlH_4$ reduction of 3,3,3-tris(4-chloropropionic acid) (Aldrich) followed by tosylation of the formed alcohol]; **17)** 3-(2-naphthyl)-3-phenyl)propanol *p*-toluenesulfonate [prepared by Horner-Emmons reaction of the sodium ylide of triethyl phosphonoacetate with 2-benzoylnaphthalene (Aldrich) followed by catalytic hydrogenation of the intermediate α,β-unsaturated ester, $LiAlH_4$ reduction and tosylation of the formed alcohol]; **18)** 3,3,3-triphenylpropanol *p*-toluenesulfonate [prepared by $LiAlH_4$ reduction of 3,3,3-triphenylpropionic acid (Aldrich) followed by tosylation of the formed alcohol]; **19)** 3-(4-phenylphenyl)-3-phenylpropanol *p*-toluenesulfonate [prepared by Horner-Emmons reaction of the sodium ylide of triethyl phosphonoacetate with 4-benzoylbiphenyl (Aldrich) followed by catalytic hydrogenation of the intermediate α,β-unsaturated ester, $LiAlH_4$ reduction and tosylation of the formed alcohol]; **20)** 1,2-diphenylbutan-1,4-diol *p*-toluenesulfonate [prepared by C-alkylation of deoxybenzoin (Aldrich) with ethyl bromoacetate (Aldrich) followed by $LiAlH_4$ reduction of the intermediate β-ketoester and tosylation of the formed diol]; **21)** 3-phenyl-3-(4-trifluoromethylphenyl)propanol *p*-toluenesulfonate prepared by Horner-Emmons reaction of the sodium ylide of triethyl phosphonoacetate with 4-(trifluoromethyl)benzophenone (Aldrich) followed by catalytic hydrogenation of the intermediate α,β-unsaturated ester, $LiAlH_4$ reduction and tosylation of the formed alcohol]; **22)** 3-chloro-1-(4-*tert*-butylphenoxy)-1-(4-fluorophenyl)propane [prepared analogously to the method of U.S. Pat. 5,281,624 by reduction of 3-chloro-4'-fluoropropiophenone (Aldrich) with 1.0 M borane-tetrahydrofuran complex ("BTC", Aldrich) followed by Mitzunobu reaction (diethyl azodicarboxylate ("DEAD"), Ph_3P, see Example 8C, Step 1) of the resulting alcohol with 4-*tert*-butylphenol (Aldrich)]; **23)** 3-chloro-1-(2-methyl-5-pyridyloxy)-1-phenylpropane [prepared by reduction of 3-chloropropiophenone (Aldrich) with 1.0 M BTC followed by Mitzunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 5-hydroxy-2-methylpyridine (Aldrich)]; **24)** 3-chloro-1-(4-phenylphenoxy)-1-(4-fluorophenyl)propane [prepared by reduction of 3-chloro-4'-fluoropropiophenone with 1.0 M BTC followed by Mitzunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 4-phenylphenol (Aldrich)]; **25)** 3-chloro-1-(4-*tert*-octylphenoxy)-1-phenylpropane [prepared by reduction of 3-chloropropiophenone with 1.0 M BTC followed by Mitzunobu reaction (DEAD, Ph_3P) of the resulting alcohol with 4-*tert*-butylphenol]; **26)** (*R*)-(+)-3-chloro-1-(4-phenylphenoxy)-1-phenylpropane [prepared by Mitzunobu reaction (DEAD, Ph_3P) of (R)-(+)-3-chloro-1-phenyl-1-propanol (Aldrich) with 4-phenylphenol (Aldrich)(see, e.g., U.S. Pat. 5,068,432) (Reaction illustrated in Fig. 3, Reaction 27)]; Compound A61 was prepared